UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/374,967	08/16/1999	KANWARPAL S. DHUGGA	5718-55	4392

27310 7590 11/21/2002

PIONEER HI-BRED INTERNATIONAL INC.
7100 N.W. 62ND AVENUE
P.O. BOX 1000
JOHNSTON, IA 50131

EXAMINER
KUBELIK, ANNE R

ART UNIT	PAPER NUMBER
1638	18

DATE MAILED: 11/21/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/374,967	DHUGGA ET AL.	
	Examiner	Art Unit	
	Anne R. Kubelik	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5,7-13,23,24,32,33 and 41-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,7-13,23,24,32,33 and 41-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The finality of the rejection of the last Office action is withdrawn in light of the new rejections below.

2. Claims 1, 3-5, 7-13, 23-24, 32-33 and 41-45 are pending.

Claim Objections

3. Claim 11 objected to because there should be no colon after "of" in line 2.

Claim Rejections - 35 USC § 101

4. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

5. Claim 45 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims are drawn to seed, which is a product of nature.

Claim 45, as written, do not sufficiently distinguish over seeds as they exist in nature because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. See *American Wood v. Fiber Disintegrating Co.*, 90 U.S. 566 (1974), *American Fruit Growers v. Brogdex Co.*, 283 U.S. 2 (1931), *Funk Brothers Seed Co. v. Kalo Inoculant Co.*, 33 U.S. 127 (1948), *Diamond v. Chakrabarty*, 206 USPQ 193 (1980). It is suggested that the claims be modified to refer to the hand of the inventor, *e.g.* by indicating that the seeds have the nucleotide sequence stably incorporated into their genome. See MPEP 2105.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1, 3-5, 7-13, 23-24, 32-33 and 41-45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acids of SEQ ID NO:1, does not reasonably provide enablement for a multitude of nucleic acids that encode maize or legume GDP-mannose pyrophosphorylase, that encode SEQ ID NO:2, that have 90% identity to SEQ ID NO:1, or that encode an antisense RNA of one of those nucleic acids, and plants transformed with those nucleic acids in a sense or antisense orientation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The rejection is modified from the rejection set forth in the Office action mailed 2 January, 2002. Applicant's arguments filed 6 August, 2002, have been fully considered but they are not persuasive.

The claims are broadly drawn to a multitude of nucleic acids that encode maize or legume GDP-mannose pyrophosphorylase, that encode SEQ ID NO:2, that have 90% identity to SEQ ID NO:1, or that encode an "antisense RNA" of one of those nucleic acids, and plants transformed with those nucleic acids in a sense or antisense orientation.

The instant specification, however, only provides guidance for random sequencing of a maize cDNA library and comparison of the sequences to sequence databases to identify a clone

(SEQ ID NO:1, which encodes SEQ ID NO:2) with homology to *Saccharomyces cerevisae* VIG9 GDP-mannose pyrophosphorylase (example 1) and general guidance for transformation of maize (example 2).

The instant specification fails to provide guidance for the isolation of construction of nucleic acids that encode legume GDP-mannose pyrophosphorylases, that have 90% identity to SEQ ID NO:1, or that encode an "antisense RNA" of one of those nucleic acids or SEQ ID NO:1, and plants transformed with those nucleic acids in a sense or antisense orientation.

The instant specification fails to provide guidance for the exact hybridization or amplification conditions and probes/primers to use in isolation of nucleic acids other than SEQ ID NO:1.

The specification on pg 7, line 11, to pg 8, line 4, suggests making conservative substitutions in SEQ ID NO:2 to make nucleic acid that encode variants. However, making "conservative" substitutions (*e.g.*, substituting one polar amino acid for another, or one acidic one for another) does not produce predictable results. Lazar et al (1988, Mol. Cell. Biol. 8:1247-1252) showed that the "conservative" substitution of glutamic acid for aspartic acid at position 47 reduced biological function of transforming growth factor alpha while "nonconservative" substitutions with alanine or asparagine had no effect (abstract). Similarly, Hill et al (1998, Biochem. Biophys. Res. Comm. 244:573-577) teach that when three histidines that are maintained in ADP-glucose pyrophosphorylase across several species are substituted with the "nonconservative" amino acid glutamine, there is little effect on enzyme activity, while the substitution of one of those histidines with the "conservative" amino acid arginine drastically reduced enzyme activity (see Table 1). All these mutated proteins, however, would have at least

95% identity to the original protein. The nucleic acids encoding all these mutated proteins, however, would hybridize under high stringency to the nucleic acids encoding the original protein.

Given the claim breath, unpredictability, and lack of guidance as discussed above, undue experimentation would have been required by one skilled in the art to develop and evaluate nucleic acids with 90% identity to SEQ ID NO:1. Making all possible single nucleotide substitutions in an 1086 nucleotide long nucleic acid like SEQ ID NO:1 would require making and analyzing 3^{1086} nucleic acids; these nucleic acids would have 99.9% identity to SEQ ID NO:1. Because nucleic acids with 90% identity to SEQ ID NO:1 would have 108 nucleotide substitutions, many more than 3^{1086} nucleic acids would need to be made and analyzed.

The claims are drawn to all nucleic acids that have 90% identity to SEQ ID NO:1. However, not all of these nucleic acids will encode a functional protein. The specification does not teach how to use nucleic acids that do not encode a functional protein.

As the specification does not describe the transformation of any plant with a nucleic acid with 90% identity to SEQ ID NO:1, undue trial and error experimentation would be required to screen through the myriad of nucleic acids encompassed by the claims and plants transformed therewith, to identify those with gum overproduction or dwarf phenotype, if such plants are even obtainable.

The specification on pg 3, lines 12-19, describes plants transformed with a construct comprising the GDP-mannose pyrophosphorylase DNA in an antisense orientation as having a decrease in protein glycosylation, and thus inhibited cell growth and a dwarf phenotype. Keller et al (1999, Plant J. 19:131-141) transformed potato plants with the potato GDP-mannose

pyrophosphorylase cDNA in the antisense orientation and found that while those plants had reduced levels of ascorbic acid and mannose, they had no detectable alteration in protein glycosylation or major carbohydrate levels (pg 133-136). Additionally, the plants did not display dwarfing, but the aerial parts of the plants died after three months in soil (paragraph spanning pg 136-137).

Additionally, antisense constructs that are not completely homologous to the target gene can have very unpredictable effects. Colliver et al (1997, Plant Mol. Biol. 35:509-522) showed that transformation of bird's foot trefoil with a construct that was antisense to bean chalcone synthase resulted in transformants with *increased* levels of chalcone synthase transcripts (pg 519, left column, paragraph 2) and note other instances when this phenomenon has occurred (pg 519, right column, paragraph 1).

Given the claim breath, unpredictability in the art, undue experimentation, and lack of guidance in the specification as discussed above, the instant invention is not enabled throughout the full scope of the claims.

Applicant urges that the specification provides sufficient support to enable one of skill in the art to isolate and ascertain the function of the claimed sequences without undue experimentation, given the description of standard PCR and hybridization protocols on pg 8-12 of the specification. Applicant urges that Examiner has confused repetition with undue experimentation (response pg 9-14).

This is not found persuasive because the specification fails to describe sequence motifs critical for enzymatic function or how to assay for GDP-mannose pyrophosphorylase activity. Additionally, Hill et al teaches that making substitutions based on amino acid sequence

comparisons is very unpredictable, as discussed above. The specification only provides general guidance for methods of hybridization isolation of genes by PCR and does not describe the exact hybridization conditions and PCR primers needs to isolate the claimed nucleic acids. Lastly, description of the phenotype of plants transformed with antisense constructs of GDP-mannose pyrophosphorylase provided by the specification on pg 3, lines 12-19, does not match the phenotype of plants transformed with antisense constructs of GDP-mannose pyrophosphorylase described in the post-filing publication by Keller et al, as discussed above.

8. Claims 1, 3-5, 7-13, 23-24, 32-33 and 41-45 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is modified from the rejection set forth in the Office action mailed 2 January, 2002. Applicant's arguments filed 6 August, 2002, have been fully considered but they are not persuasive.

The claims are broadly drawn to a multitude of nucleic acids that encode maize or legume GDP-mannose pyrophosphorylase, that have 90% identity to SEQ ID NO:1, or that encode an antisense RNA of one of those nucleic acids, and plants transformed with those nucleic acids in a sense or antisense orientation, wherein the nucleic acids are from any source. In contrast, the specification only describes a coding sequence from maize that comprises SEQ ID NO:1. Applicant does not describe other nucleic acids encompassed by the claims, including those from legumes or that encode other maize GDP-mannose pyrophosphorylases, and the structural features that distinguish all such nucleic acids from other nucleic acids are not provided.

The claims include no description the protein encoded by nucleic acids that have 90% identity to SEQ ID NO:1.

Additionally, the phenotype of plants transformed with antisense constructs of GDP-mannose pyrophosphorylase described in the specification on pg 3, lines 12-19, does not match the phenotype of plants transformed with antisense constructs of GDP-mannose pyrophosphorylase as described by Keller et al, as discussed above.

Hence, Applicant has not, in fact, described nucleic acids that encode maize or legume GDP-mannose pyrophosphorylase, that have 90% identity to SEQ ID NO:1, or that encode an "antisense RNA" of one of those nucleic acids within the full scope of the claims, or plants transformed with those nucleic acids in a sense or antisense orientation, and the specification fails to provide an adequate written description of the claimed invention.

Therefore, given the lack of written description in the specification with regard to the structural and physical characteristics of the claimed compositions, it is not clear that Applicant was in possession of the genus claimed at the time this application was filed.

See *Univ. of California v. Eli Lilly*, 119 F.3d 1559, 43 USPQ 2d 1398 (Fed. Cir. 1997):

> The name cDNA is not in itself a written description of that DNA; it conveys no distinguishing information concerning its identity. While the example provides a process for obtaining human insulin-encoding cDNA, there is no further information in the patent pertaining to that cDNA's relevant structural or physical characteristics; in other words, it thus does not describe human insulin cDNA .... Accordingly, the specification does not provide a written description of the invention ....

and at pg 1406:

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicted, does not suffice to define the genus because it is only an indication of what the genes does, not what it is.

See *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ 2d 1016 at page 1021:

> A gene is a chemical compound, albeit a complex one, and ... conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials .... Conception does not occur unless one has a mental picture of the structure of the chemical or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by it principal biological property, *e.g.*, encoding human erythropoietin, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property.

Applicant urges that the invention is described functionally and structurally and not merely by a method of making coupled with a function. Applicant urges that the claimed invention is described by function - that they must function as plant GDP-mannose pyrophosphorylases (specification, pg 4, lines 15-17) - and as having 90% identity to SEQ ID NO:1 or as hybridizing to SEQ ID NO:1. Thus, Applicant urges that the physical and chemical properties of the claimed sequences are described (response pg 3-9).

This is not found persuasive because the specification does not describe the sequence nucleic acid that encode legume GDP-mannose pyrophosphorylase or other maize GDP-mannose pyrophosphorylases. Additionally, the claims are not drawn to nucleic acids that have 90% identity to SEQ ID NO:1 and encode a GDP-mannose pyrophosphorylase, but are solely drawn to nucleic acids that have 90% identity to SEQ ID NO:1. Lastly, description of the phenotype of plants transformed with antisense constructs of GDP-mannose pyrophosphorylase provided by the specification on pg 3, lines 12-19, does not match the phenotype of plants transformed with antisense constructs of GDP-mannose pyrophosphorylase described by Keller et al, as discussed above.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 3-4 11 and 32-45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention. Dependent claims are included in all rejections.

Claim 3 lacks antecedent basis for the limitation "said GDP-mannose" in line 1.

Claims 4 and 8 lack antecedent basis for the limitation "said leguminous plant" in line 1

Claim 11 is not written in proper Markush format. The claims should be in the format "selected from the group consisting of A, B, C and D." The phrase "of promoters" should not be located after "group of". See MPEP § 2173.05(h).

In claim 32, --wherein-- should be inserted before "said" in line 3.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a), which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 23, 32 and 41-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over each of Gordon-Kamm et al (1990, Plant Cell 2:603-618) and Facciotti et al (1985, BioTechnology 3:241-246) in view of Hashimoto et al (1997, J. Biol. Chem. 272:16308-16314), further in view of Wheeler et al (1998, Nature 393:365-369).

The claims are drawn to plants and plant cells transformed with a nucleic acid encoding GDP-mannose pyrophosphorylase operably linked to a plant promoter.

Gordon-Kamm et al disclose transformation of maize with a construct comprising a nucleic acid encoding GUS operably linked to a plant promoter (pg 615-616) and seeds produced from the transformed plants (pg 609). Gordon-Kamm et al do not disclose maize plants transformed with a nucleic acid encoding GDP-mannose pyrophosphorylase.

Facciotti et al disclose transformation of soybean with a construct comprising a nucleic acid encoding kanamycin resistance operably linked to a plant promoter (figure 2, pg 244). Facciotti et al not disclose soybean plants transformed with a nucleic acid encoding GDP-mannose pyrophosphorylase.

Hashimoto et al teach a nucleic acid encoding the *S. cerevisae* GDP-mannose pyrophosphorylase (pg 16310, left column, paragraph 2, to right column, paragraph 3).

Wheeler et al teach that GDP-mannose pyrophosphorylase plays a crucial role in the plant vitamin C biosynthetic pathway (Figure 4).

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to modify the method of plant transformation as taught by each of Gordon-Kamm et al and Facciotti et al, to transform plants with a nucleic acid encoding the GDP-mannose pyrophosphorylase described in Hashimoto et al. One of ordinary skill in the art would have been motivated to do so because of the role GDP-mannose pyrophosphorylase in vitamin C biosynthesis (Wheeler et al, Figure 4) and to increase vitamin C content of plants.

13. Claims 1, 3-5, 7-13, 24, 33 and 41-45 are free of the prior art, given the failure of the prior art to teach or suggest an isolated nucleic acid that encodes a maize or legume GDP-mannose pyrophosphorylase, that encode SEQ ID NO:2, that have 90% identity to SEQ ID

NO:1, or that encode an "antisense RNA" of one of those nucleic acids, and plants transformed with those nucleic acids.

Conclusion

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, whose telephone number is (703) 308-5059. The examiner can normally be reached Monday through Friday, 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at (703) 306-3218. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Customer Service at (703) 308-0198.

Anne R. Kubelik, Ph.D.
November 15, 2002

AMY J. NELSON, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600